REMARKS

The Applicant has received and carefully reviewed the Office Action dated March 25, 2008.

Claims 1-10 and 18-26 are withdrawn, and claims 11-17 are currently pending. Claims 11, and 13-15 are amended to further refine and clarify that which Applicant considers to be the invention. No new matter has been added by these amendments.

Claim Objections

The Examiner objected to claims 1-10 and 18-25, because the claims did not have the proper claim status identifiers. Applicant has corrected the status identifiers of the withdrawn claims, and as such, the Examiner's objection is now moot.

The Examiner also objected to claims 13 and 15 because the Examiner contends that the abbreviation "HCEC" is not a commonly understood term in the art. Applicant notes that the abbreviation stands for "human corneal endothelial cell", and is explicitly defined in the specification at paragraph [0011]. Furthermore, if one searches the term "human corneal endothelial

cell" on the GOOGLE™ website, the search results show that many scientific authors have used this abbreviation. As such, Applicant submits that the term "HCEC" as used in the specification and claims is clear and unambiguous, and Applicant respectfully requests withdrawal of this objection.

Rejections under 35 U.S.C. §112, second paragraph

The Examiner rejected claims 11-17 as indefinite, for reciting the term "RGDS" without a reference to a precise amino acid sequence. Applicant respectfully traverses this rejection.

RGDS is a tetrapeptide that is well known as a reagent for cellular attachment. The letters R, G, D, and S are the single-letter amino acid code representing arginine, glycine, aspartic acid, and serine. Applicant has included with this response, a page from the Sigma-Aldrich Product Catalog, where this tetrapeptide is commercially available, and shows that RGDS is a commonly used synonym for this peptide (Attachment A).

Furthermore, while it is apparent that under the sequence listing rules at 37 CFR §1.821, an amino acid sequence of four amino acids would ordinarily require a SEQIDNO and a sequence

listing, exceptions are made when the peptide is a recognized cellular reagent, such as RGDS. See, for example, U.S. Patent Nos. 5,853,713; 7,052,711 and 7,090,496, where the term RGDS was used in the specification and claims without the need for a SEQIDNO or sequence listing. Applicant has amended the specification at paragraph [0013] to specifically identify the four amino acids in Applicant's first use of the term. As such, Applicant requests withdrawal of the rejection.

The Examiner also argued that the terms "approximately" "average" and "desired" are indefinite because they do not provide sufficient scope for one of skill in the art to ascertain the metes and bounds of the claimed invention. Applicant respectfully traverses this rejection.

With regard to the term "desired", Applicant has deleted the term from the claims to further clarify the invention.

Applicant submits that the other rejected terms "approximately" and "average" with respect to corneal thickness are well understood by those of skill in the ophthalmological sciences. One of ordinary skill can search any medical textbook to find what the average corneal thickness is for a human, and for many species

of mammals and animals. Therefore, the metes and bounds of Applicant's claim is clearly defined by Applicant's claim language.

With regard to the term "approximately", it is proper to use such a term in a claim when it qualifies a range or variable, such as the thickness of a cornea. See, Ex parte Shelton, 92 USPQ 374, 375 (PTO Bd. App. 1950)(stating that the use of the terms "about" or "approximately" does not subject the claims to a rejection as failing to define the invention with particularity); Ex parte Shea, 171 USPQ 383 (PTO Bd. App. 1970)(stating that a range of proportions disclosed in an application is not rendered indefinite when qualified by "approximately" in claims). Applicant therefore respectfully requests withdrawal of these rejections.

Rejections under 35 U.S.C. §102(b)

The Examiner rejected claims 11-13 and 17 under 35 U.S.C. §102(b), as anticipated by USP 5,827,641 to Parenteau et al. According to the Examiner, Parenteau et al. teach an artificial corneal transplant support and transplant, comprising a biopolymer with attachment factors, is in the shape of a cornea, and has an inner endothelial layer. Applicant respectfully traverses this rejection.

Parenteau et al. teach a complete artificial corneal construct having an endothelial cell layer, an acellular layer of collagen, a second collagen layer containing keratocytes, and a layer of epithelial cells (col. 5, line 21 - col. 7, line 66, and Figs 11A - 11D). A careful reading of Parenteau et al. reveals that human corneal endothelial cells are not used in the artificial cornea. The source of the endothelial cells are sheep, rabbit or cow cornea, or from a transformed mouse corneal endothelial cell line. Parenteau et al. also contemplates the use of non-corneal endothelial cells (col. 5, line 61 - col. 6, line 42). Nowhere in Parenteau is there any mention of human corneal endothelial cells (HCEC) as claimed by Applicant.

Moreover, with regard to the biopolymer support, Parenteau et al. does not teach incorporation of any of any attachment reagents, as claimed by Applicant, in the base biopolymer. Finally, Parenteau et al. does not teach that the support is made in the shape of a cornea, merely that it is grown in a cell culture dish.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently

described, in a single prior art reference." Verdegaal Bros. v. Union Oil Co. of California, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Parenteau et al. do not teach each and every element of Applicant's amended claims, and therefore they cannot be anticipated under 35 U.S.C. §102(b). As such, Applicant respectfully requests withdrawal of the rejection.

Rejections under 35 U.S.C. §103(a)

The Examiner also rejected claims 11-17 under 35 U.S.C. §103(a), as unpatentable, over Parenteau et al., in view of USP 6,645,715 to Griffith et al., and USP 6,689,165 to Jacob et al. According to the Examiner, Parenteau et al. fail to teach a half-thickness corneal support as recited in claims 14-16, and also fails to teach any of the attachment factors claimed by Applicant. Griffith et al. is offered by the Examiner for teaching the attachment factors such as laminin, fibronectin, bFGF and the like. The Examiner offers Jacob et al. for teaching that epithelial cell adhesion is augmented by growth factors on the polymer surface of an artificial corneal construct. The Examiner then concludes that it would have been obvious to one of ordinary skill in the art, at the time the invention was made, to modify the construct of Parenteau et al., with the attachment factors of Griffith et al.

and Jacob et al. to arrive at Applicant's claimed invention. Applicant respectfully traverses this rejection.

Griffith et al. teach an in-vitro, avascular, human corneal equivalent, comprising immortalized human cell lines, not a corneal biopolymer support suitable for transplant into a patient (abstract, col.7 - col. 8). All the teachings or examples in Griffith et al., where a biopolymer support suitable for long term growth of HCEC is produced, use only immortalized cells. Moreover, because the construct of Griffith et al. is for in-vitro testing, there is no teaching of shaping the biopolymer for use in a cornea.

Jacob et al. teach an ocular device comprising an optical polymer having biocompatible linear, single chain tether molecules having two ends, attached to the optical polymer on one end of the tether, and another corneal enhancer molecule attached to the tether at the other end. The optical polymer can be collagen, polyurethanes, polymethacrylates and other biocompatible polymers with a refractive index suitable for a cornea. The enhancer molecules can be various growth factors, such as fibronectin, laminin, EGF and other factors. It is important to note that the device of Jacob et al. is designed for growth of corneal epithelial cells on the convex surface of the device. In contrast,

Applicant's invention is directed to an artificial stroma for growth of corneal endothelial cells on the concave or inside surface of the cornea. The cell type taught in Jacob et al. is completely different than the cell type used by Applicant. One of the advantages of using endothelial cells and orienting the endothelial cells in Applicant's manner, is that the cells act as a barrier to fluid from the anterior chamber of the eye moving into the stroma, and causing stromal swelling and loss of clarity.

Jacob et al. also teach that the corneal enhancer molecules must be tethered to the optical polymer via a linear polyethylene oxide (PEO) molecule, or amino acid or peptide, with a molecular weight between 2000-8000. The synthesis of corneal enhancer molecules includes their covalent linkage to polyethylene glycol molecules, and then covalently linking these to an optical polymer substrate. It is also important to point out that Applicant's invention does not include the use of "tether molecules" as described in Jacob et al. at all.

In contrast, Applicant's invention comprises a mixture of attachment proteins, such as those identified as corneal enhancer molecules, like laminin, b-FGF, and EGF coated onto the corneal substrate. While Applicant may use b-FGF, and EGF that is

conjugated onto polycarbophil (a synthetic polymer the calcium salt of polyacrylic acid cross-linked with divynyl glycol), the conjugated growth factors are not covalently bonded to the stroma or any synthetic or natural biopolymer. In other words, they are not "tethered". The stroma of Applicant's invention is either coated with the attachment factors for a period of time, or the attachment factors are mixed with the pre-polymers before polymerization.

Applicant submits that one of ordinary skill in the art, in an attempt to improve corneal endothelial grafts, when reading Parenteau et al. in view of Griffith et al. and Jacob et al., would not have expected that Applicant's invention would work, because Jacob et al. teach that the growth factors must be covalently bound to the optical polymer to allow cell growth. Further, Griffith et al. teach that only transformed endothelial cells are able to maintain sustained growth in culture. Applicant has shown that this is not the case. In addition, Jacob et al. teaches the use of epithelial cells on outer or convex surface of the cornea, not the use of endothelial cells on the inner, or concave surface. The combination of attachment factors do not have to be covalently bound, but only coat the surface where the cells will attach, to be effective. Applicant's claimed method is simpler and more

effective and less costly, as there are no synthesis steps for making the tethered growth factors. Moreover, Applicant's cornea will not be susceptable to eventual swelling and loss of clarity.

In view of the foregoing, Applicant submits that the combination of Parenteau et al., in view of Griffith et al. and Jacob et al. does not make Applicant's claimed invention *prima facie* obvious, because: 1) the combination of references does not teach each and every element of Applicant's claimed invention, namely, the combination of references does not teach both the use of non-transformed human corneal endothelial cells, and the use of a biopolymer shaped as a cornea; and 2) the combination of references teaches away from Applicant's invention because the primary reference of Parenteau et al. and Griffith et al. are directed to immortalized human corneal endothelial cells, not cells from a patient, and Jacob et al. is directed to a completely differnent corneal cell type. Therefore Applicant respectfully requests withdrawal of this rejection.

Should the Examiner have any questions or believe an interview would expedite prosecution of the instant application; the Examiner is invited to telephone undersigned counsel.

Respectfully submitted,

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ProductInformation

Arg-Gly-Asp-Ser

Product Number **A 9041**
Storage Temperature -0 °C

Product Description
Molecular Formula: $C_{15}H_{27}N_7O_8$
Molecular Weight: 433.4
CAS Number: 91037-65-9
Synonym: L-arginyl-glycyl-L-aspartyl-L-serine, RGDS

The tetrapeptide Arg-Gly-Asp-Ser (RGDS) is a key component of the cell attachment domain of fibronectin. The RGDS sequence was found initially to promote the attachment of rat kidney fibroblasts (NRK cells) to fibronectin and synthetic fibronectin peptides coupled to protein-coated plastic. Further investigation indicated that the free RGDS peptide inhibited the attachment of NRK cells to fibronectin coated substrates. The RGDS sequence has been shown to occur in several other proteins, such as the λ receptor on *E. coli* and the Sindbis coat protein.[1] RGDS is also a target sequence for spirochete adherence of the syphilis bacterium *Treponema pallidum*.[2]

RGDS has been shown to block fibrinogen-induced aggregation of intact erythrocytes and specific binding of fibrinogen to erythrocyte membranes.[3] The effect of RGDS on transforming growth factor β1 (TGFβ1) mRNA expression and secretion in cultured human mesangial cells has been investigated.[4] RGDS has been utilized in a study of integrin-mediated signal transduction in cultured cells from the sponge *Suberites domuncula*.[5] RGDS has been demonstrated to mitigate the binding of *Mycobacterium tuberculosis* to murine alveolar macrophages.[6]

Precautions and Disclaimer
For Laboratory Use Only. Not for drug, household or other uses.

Preparation Instructions
This product is soluble in water (1 mg/ml), yielding a clear, colorless solution.

References
1. Pierschbacher, M. D., and Ruoslahti, E., Cell attachment activity of fibronectin can be duplicated by small synthetic fragments of the molecule. Nature, **309(5963)**, 30-33 (1984).
2. Thomas, D. D., et al., Fibronectin tetrapeptide is target for syphilis spirochete cytadherence. J. Exp. Med., **162(5)**, 1715-1719 (1985).
3. Lominadze, D., and Dean, W. L., Involvement of fibrinogen specific binding in erythrocyte aggregation. FEBS Lett., **517(1-3)**, 41-44 (2002).
4. Ortega-Velazquez, R., et al., Arg-Gly-Asp-Ser (RGDS) peptide stimulates transforming growth factor β1 transcription and secretion through integrin activation. FASEB J., **17(11)**, 1529-1531 (2003).
5. Wimmer, W., et al., Origin of the integrin-mediated signal transduction. Functional studies with cell cultures from the sponge *Suberites domuncula*. Eur. J. Biochem., **260(1)**, 156-165 (1999).
6. Pasula, R., et al., Fibronectin facilitates *Mycobacterium tuberculosis* attachment to murine alveolar macrophages. Infect. Immun., **70(3)**, 1287-1292 (2002).

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